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VERIFICATION OF A TRANSLATION

I, Charles Edward SITCH BA,

Deputy Managing Director of RWS Group Ltd UK Translation Division, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare:

That the translator responsible for the attached translation is knowledgeable in the French language in which the below identified international application was filed, and that, to the best of RWS Group Ltd knowledge and belief, the English translation of the international application No. PCT/FR2003/003628 is a true and complete translation of the above identified international application as filed.

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application issued thereon.

Date: June 8, 2005

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METHOD FOR ACQUIRING ELECTROMAGNETIC SIGNALS AND CONTRAST PRODUCT THEREFOR

The present invention relates to the acquisition of electromagnetic signals. It relates more particularly to the acquisition of such signals received from a body part, in particular a human or animal body part, in response to an external electromagnetic solicitation.

Various methods for acquiring signals are known, in particular in the magnetic resonance imaging (MRI) field. These methods have common characteristics.

They generally consist in subjecting the body in question to a high-intensity magnetic induction B_0, typically between 0.1 and 3 Tesla. The effect of this induction is to orient the magnetic moments of the protons of the hydrogen contained in the water molecules of the body in a direction close to the main direction of the magnetic induction B_0.

The body part imaged is then subjected to a radiofrequency wave applied perpendicular to the magnetic induction B_0 and the frequency of which is typically adjusted to the Larmor precession frequency of the hydrogen nucleus in the magnetic induction B_0 in question. This frequency is proportional to the intensity of the magnetic induction B_0 and has the specificity of bringing into resonance the protons of the hydrogen contained in the water molecules of the body. By way of example, for an induction B_0 of 1 Tesla, the corresponding Larmor frequency is in the region of 42 MHz.

Immediately after the transmission of this radio frequency wave, the magnetic moments that have been subjected to the wave begin to oscillate around their equilibrium position and again take up a position along

their original direction, close to that of the magnetic induction B_0. This phenomenon is known as proton relaxation.

During the relaxation, each water proton that has come into resonance creates, as a result, a relatively weak electromagnetic signal, called a magnetic resonance signal. This signal can then be detected by means of an appropriate detection module.

Gradients of the magnetic induction B_0 can be used in various spatial directions, so as to have different induction values between two points in space, each corresponding to an elementary volume of the body in question.

The use of magnetic induction B_0 gradients therefore allows spatial localization of the signal. The step of coding the space by means of the gradients is carried out between the proton excitation and the magnetic resonance signal reception.

These basic principles give rise to different methods of exploitation so as to allow the production of a selective image for a chosen element of the body observed, for example a blood vessel.

In a first method, referred to as "time of flight" method, the radio frequency waves are transmitted repeatedly and regularly, in a train of pulses. The repetition of these waves is adjusted so as to be sufficiently frequent for the proton relaxation not to have time to be entirely complete before transmission of the next wave. This saturation phenomenon means that the magnetic resonance signal is greatly reduced. It virtually makes it possible to eliminate the signals transmitted by the immobile protons, i.e. typically the protons that are part of tissues of the body in question.

On the other hand, mobile protons that penetrate the zone in question without having been subjected beforehand to a train of pulses come into resonance and create a magnetic resonance hypersignal that can be detected. The mobile protons are typically the protons contained in the water of the circulating blood.

This time of flight method therefore makes it possible to distinguish between the relaxed mobile protons and the saturated immobile protons and thus makes it possible to isolate a selective signal corresponding, for example, to a blood activity. This method can in particular be applied in the field of angiography, since it makes it possible to detect a signal originating from a blood vessel in particular.

It is, however, limited to the analysis of blood vessels that are short and have a high flow rate, since, if the opposite is true, the protons contained in the blood circulating in these vessels rapidly undergoes saturation, like the protons of the surrounding tissues.

A second method, referred to as "phase contrast" method, takes advantage of the relationship that exists between the phase of the detected magnetic resonance signal and the rate of proton displacement in the body in question, to allow detection of blood vessels within the body. However, this method has drawbacks insofar as a prior estimation of the rate of circulation in the vessels is necessary. In addition, since the phase is a quantity expressed to within 2π, an ambiguity remains regarding the effective rate deduced from a magnetic resonance signal.

These first two methods are therefore based on characteristics associated with a displacement, in particular of blood in the body. They thus find an

application in the angiography field. On the other hand, they do not make it possible to detect a particular static or virtually static element of the body. They cannot therefore be used as a basis for the formation of an image for a particular organ or for a particular cell type.

A third method has made a name for itself in the last few years in the angiography field. It comprises a step consisting in injecting a contrast product into a body. In general, the contrast product used is gadolinium attached to a chelating agent such as DOTA (or tetraazacyclododecane tetraacetate) or DTPA (or diethylenetriamine pentaacetate). The chelating agent is a molecular cage that surrounds the gadolinium and makes it possible to limit its toxicity with respect to the body into which it is injected. The effect of this product is to decrease the relaxation time of the protons that are in proximity. Specifically, the contrast product contains single unpaired electrons which have a paramagnetic effect that acts on the water protons.

This increase in proton relaxation makes it possible to limit the saturation in the zone where the injected product is located. The resulting magnetic resonance signal is therefore greatly increased. Conversely, the protons that are not in immediate proximity to the gadolinium keep an unchanged relaxation time and therefore generate a lower magnetic resonance signal.

Initially after injection, the contrast product moves in the blood vessels without being absorbed by the surrounding tissues. Detection of the magnetic resonance signals therefore makes it possible to distinguish between the blood vessels and the surrounding tissues and also to form an image revealing this distinction.

However, this technique also has drawbacks. In particular, paramagnetic gadolinium, in addition to its action on proton relaxation time, creates magnetic induction microgradients that result in local distortions of the magnetic induction to which the body is subjected. The frequencies of the waves transmitted are dispersed. This effect can result in the loss of certain signals. When the magnetic resonance signals are used to form an image of a zone of the body in question, said image will therefore be difficult to interpret. This results in the spatial resolution of the images obtained by this technique being limited: this method does not allow complete suppression of the signals derived from tissues lacking contrast product.

An object of the present invention is to provide a method for acquiring magnetic resonance signals that limits the problems encountered in the above techniques.

Another object of the invention is to enable acquisition of the signals from a selected observed zone, independent of its type. For example, the observed zone may contain substantially mobile or substantially immobile protons. It may be a blood vessel or a vascularized network, but also an organ, a group of cells, or the like.

The invention thus proposes a method for acquiring electromagnetic signals received from at least one part of a body placed in a system comprising means for generating a magnetic induction B_0, said magnetic induction comprising gradients in certain directions in space, means for transmitting radio frequency wave pulse sequences perpendicular to the magnetic induction B_0 in a range of adjustable frequencies, and means for detecting electromagnetic signals received from said body part. The method comprises the following steps:

a) injecting, into said body part, an amount of contrast product capable of being temporarily fixed in or of passing through an observed zone of said body part, said contrast product comprising at least one element capable of causing a chemical shift of a resonance frequency of water hydrogen protons;

b) exciting said body part by means of a radio frequency wave pulse sequence in a range of frequencies adjusted according to the magnetic induction B_0 and to the chemical shift for at least some of said radio frequency waves;

c) detecting, coherently with the excitation of step b), electromagnetic signals received from said body part, said signals corresponding substantially to magnetic resonance signals of the protons of the observed zone having undergone the chemical shift.

The chemical shift provided by the contrast product brings about a shift in the resonance frequency of the hydrogen protons contained in the water in proximity to the injected contrast product. This shift in frequency makes it possible to obtain a selective signal from the protons chemically shifted during a radio frequency-based solicitation taking into account this shift. Such selective signal can advantageously be used as a basis for forming an image.

The observed zone envisioned here may be of various types, for instance a blood vessel, a group of cells expressing a gene, a tumor zone, or the like.

The invention also proposes a contrast product intended to be injected into at least one part of a body for the purpose of acquiring electromagnetic signals from said body part. This product comprises at least one element

capable of causing a chemical shift of a resonance frequency of water hydrogen protons.

The element included in the contrast product may advantageously be a lanthanide, for example dysprosium, praseodymium and/or europium, optionally attached to a chelating agent, or any other element capable of inducing a modification of the resonance frequency.

Other particularities and advantages of the present invention will emerge from the following description of nonlimiting implementation examples, with reference to the attached drawing in which the single figure is a simplified representation of an observed zone to which the invention is applied.

According to the invention, an amount of contrast product is injected into a body 4, which may be, for example, a human or animal body, but which may also be an inert body. The injection is performed in such a way that the contrast product is fixed at least temporarily in or passes through an observed zone 1. In the case of a human body, for example, the contrast product may be injected intravenously. The observed zone may then comprise a blood vessel 2 through which the contrast product passes, and also the tissues 3 that surround this vessel.

The various steps of the method described below must take place rapidly after injection of the contrast product so that the latter remains essentially contained in the zone for which it is desired to recover a magnetic resonance signal, i.e., in the example illustrated in the figure, the vessel 2, but not the tissues 3 that surround it.

The contrast product used according to the invention has the property of effecting a chemical shift on the hydrogen protons that are in proximity thereto. This is

because such a product contains atoms whose electron cloud is capable of modifying the local magnetic induction experienced by the nucleus observed. The protons that are in proximity to the contrast product, for example the protons contained in the hydrogen of the water of the blood circulating in the vessel 2, are subjected to this magnetic induction.

If the protons in contact with the contrast product are subjected to a magnetic induction B_0, their resonance frequency is no longer the Larmor frequency ν_0 proportional to the amplitude of B_0, but a frequency ν_1 that is shifted with respect to ν_0. By way of illustration, if the chemical shift created by the contact product is 3.5 parts per million (ppm), the following frequency relationship is obtained: $\nu_1 - \nu_0 = 3.5 \times 10^{-6} \times \nu_0$. For a magnetic induction $B_0 = 1.5$ T, the Larmor frequency $\nu_0 = 63$ MHz, and a frequency shift $\nu_1 - \nu_0 \approx 220$ Hz is therefore obtained between the protons that are in proximity to or not in proximity to the contrast product.

It should be noted that the chemical shift property is not inherent to all products. In particular, gadolinium, commonly used as a contrast agent for its properties of reducing the proton relaxation time as explained in the introduction, causes virtually no chemical shift. On the other hand, three other elements of the lanthanide family are notable for their chemical shift action. These are dysprosium (Dy), praseodymium (Pr) and europium (Eu).

For example, as regards dysprosium, the chemical shift created Δ (in ppm) is proportional to the concentration of dysprosium (in millimoles per liter) with a proportionality coefficient of 0.185, i.e. $\Delta = 0.185*[Dy]$.

Conventionally, cages are used to surround the

lanthanides in order to limit their toxicity, as was the case for gadolinium. These cages are typically chelating agents such as DOTA or DTPA. The contrast product used is therefore advantageously a lanthanide chelate capable of generating a chemical shift, such as Dy-DOTA, Dy-DTPA, Pr-DOTA or Pr-DTPA.

The body 4 is placed, immediately before or after injection of the contrast product, in a system that surrounds a part of the body and that is capable of generating a high-amplitude magnetic induction B_0. This induction comprises gradients in principle directions in space according to the type of information that it is desired to acquire. For example, if it is desired to obtain magnetic resonance signals for elementary volumes in three-dimensional space, it will be advisable to introduce coding gradients G_x, G_y and G_z for the magnetic induction B_0 in three main perpendicular directions (x, y, z) in space, in a manner known in itself. By means of this technique, magnetic induction values that are different between elementary volumes of the body 4 are ensured.

The system in which the body 4 is placed also has a transmitter of radio frequency wave pulse sequences in a range of adjustable frequencies that may be more or less selective, according to the duration of transmission of the corresponding waves. These RF waves are transmitted perpendicular to the direction of the magnetic induction B_0. When a wave is transmitted at a frequency corresponding to the proton resonance frequency, said protons are then taken out of their equilibrium position in a direction close to that of the induction B_0, and then they gradually return to this equilibrium position.

According to the invention, the protons in proximity to the injected contrast product have a resonance frequency that is shifted with respect to the usual

Larmor frequency. Advantage is then taken of this particularity in order to recover electromagnetic signals only from these chemically shifted protons.

For this, at least two methods can be envisioned. According to a first embodiment, a radio frequency wave pulse sequence is transmitted with a frequency adjusted selectively to the value of the frequency shifted due to the chemical shift, i.e. ν_1 according to the notation employed above.

At the end of each transmission of a radio frequency wave pulse sequence, a reception module detects and evaluates the transmitted magnetic resonance signal. According to the principle explained above, only the protons in the vessel 2 of the example illustrated in the figure come into resonance and generate a magnetic resonance signal. The other protons that are not in proximity to the injected contrast product, i.e. typically the protons present in the tissues 3, generate virtually no signal.

Thus, if an image of the observed zone 1 is realized, for example in a spatial plane, by taking advantage of the magnetic induction gradients, and with each point of the image corresponding substantially to a detected signal value, as a function of its geographical position in the plane under consideration according to a conventional spatial coding, the zones where the contrast product has been fixed can be clearly distinguished. An image is thus obtained, where the vessel 2 will be visible, while the tissues 3 will be invisible.

This embodiment is therefore entirely advantageous. However, it has the drawback of requiring a sequence of radio frequency transmissions that are selective with respect to frequency, which means that a considerable transmission time is needed. When the observed zone is

large, the signal acquisition time may prove to be disadvantageous.

A second advantageous embodiment makes it possible to limit the magnetic resonance signal acquisition time. It consists in using a radio frequency wave pulse transmission sequence comprising a first series of selective wave pulses adjusted to a frequency corresponding substantially to the Larmor frequency for the water protons not chemically shifted, i.e. the protons of the tissues 3 in the example illustrated. These waves are transmitted with a sufficient duration to saturate the protons concerned, to such an extent that these protons no longer transmit any significant magnetic resonance signal at the end of the first series of wave pulses.

The radio frequency wave transmission sequence also comprises a second series of wave pulses that are relatively nonselective in terms of frequency, each wave of the sequence being transmitted over a short period of time. The range of frequencies covered by these waves comprises the resonance frequency of the chemically shifted protons, i.e. of the protons of the vessel 2. Thus, only the latter protons will come into resonance upon transmission of the second series of waves, the protons of the tissues 3 being saturated. This makes it possible to rapidly receive the signals coming from only the protons of the vessel 2.

In this way, the signals transmitted by the chemically shifted protons are isolated with precision. Furthermore, the contrast products used with dysprosium, praseodymium or europium have only a limited action on the distortion of the magnetic induction in the observed zone, through the creation of magnetic induction microgradients, unlike gadolinium. The images obtained by applying this technique therefore potentially have a greater spatial resolution

than the known techniques using gadolinium chelates.

As was described above, the chemical shift engendered by injection of the contrast product, for example dysprosium, as a function of the concentration of the latter, is known. This prior knowledge can make it possible to precisely select the frequency of the wave to be transmitted in the observed zone. However, in another advantageous embodiment, it is possible to determine the frequency resulting from the chemical shift without prior knowledge. For this, the observed zone 1 of the body 4 is subjected to successive waves in a broad spectrum of radiofrequencies and the magnetic resonance signals generated by the observed zone in reaction to each of these waves are detected. The main frequency that causes the protons of the observed zone having undergone the chemical shift to come into resonance is then deduced therefrom.

So far, the observed zone 1, illustrated in the figure, has been taken to comprise a blood vessel 2 surrounded by tissues 3. This representation makes it possible to envision applications of the present invention in the angiography field.

However, the invention can also be applied to other types of observed zones. In particular, the observed zone may comprise a target, which may, for example, be a cell, a molecule, a protein, or a group of targets of the body under consideration, such as a group of cells expressing a gene.

In this situation, a known targeting molecule is advantageously attached to the contrast product injected into the body, such that the latter is temporarily fixed in the target. The steps described above can then be carried out so as to acquire magnetic resonance signals coming from the target only, with the exclusion of certain surrounding tissues in which the

contrast product has not been fixed. This embodiment is particularly advantageous and finds applications in the field of cellular and molecular imaging, for example for studying gene expression in vivo, for localizing a particularly biological activity, or the like.

The observed zone may also be a zone of angiogenesis, for example a tumor zone. Such a zone generally comprises a vascularized network, the vascularization index of which gives an indication regarding the malignant or benign nature of the tumor.

In one embodiment, the invention makes it possible to determine such a vascularization index. To this effect, the lanthanide chelate used as contrast product is injected so as to be temporarily fixed in the tumor zone. As described above, it is possible to realize a spectrum in this observed zone, i.e. to transmit successive radio frequency waves within a broad spectrum of frequencies. The resonance frequency of the protons located in the vascularized network present in the tumor zone is deduced therefrom, this resonance frequency being substantially the frequency for which magnetic resonance signals were received (outside the conventional Larmor frequency of the water protons not having experienced a chemical shift). Advantageously, this operation can be carried out several times at successive moments so as to make it possible to monitor any change in the time of this resonance frequency.

As was indicated above, the chemical shift caused by the contrast product, for example based on dysprosium, is proportional to the concentration of dysprosium. Determination of the resonance frequency in the tumor zone, which is itself proportional to the chemical shift, then gives an indication of the concentration of contrast product fixed in the observed zone. It is therefore understood that this indication constitutes a vascularization index that can be taken into account in

a subsequent analysis of the tumor.

As in the previous cases, the magnetic resonance signals coming from the tumor zone can be acquired so as to characterize in greater detail the vascularized network present in the tumor zone. An image of the zone can also be obtained from this acquisition.